Journal of Comprehensive Surgery

Original Article

DOI: 10.51271/JOCS-0025

Prognostic factors and survival of breast cancer in patients over 40 years of age

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Cite this article: Yüksek MA, Yürüker SS, Mutlu V. Prognostic factors and survival of breast cancer in patients over 40 years of age. *J Compr Surg.* 2024;2(1):6-11.

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Received: 26/01/2024 ◆ **Accepted**: 26/02/2024 ◆ **Published**: 28/02/2024

ABSTRACT

Aims: Breast cancer is the cancer with the highest incidence and mortality in women. There are differences in prognosis and survival between women over and under the age of 40. In this article, we aimed to examine breast cancer prognostic factors and survival results in people over the age of 40.

Methods: 1187 patients aged 40 and over who underwent surgery at the Ondokuz Mayıs University Department of General Surgery between August 2005 and April 2019 and whose data were accessible were retrospectively examined. Data were obtained from the hospital automation system, the Ministry of Health's online database, hospital archives, patients, and/or their relatives. They were classified separately in terms of type of surgery, axillary metastasis status (according to radiological status if axilla surgery is not performed), type of axilla surgery performed, pathological tumor size, number of pathological lymph nodes, pathological stage, lymphovascular and perineural invasion status, hormone receptor positivity, C-erb B2 and Ki-67 status, neoadjuvant treatment status, and molecular subgroup. Variables were analyzed individually for recurrence, mortality, and survival. Results found to be significant were subjected to multivariate analysis testing. Statistical significance was accepted as $p<0.05$.

Results: As a result of multivariate analysis performed by excluding data that disrupted homogeneous distribution, perineural invasion, lymphovascular invasion, grade, and progesterone receptor status were determined to be independent prognostic factors in terms of recurrence. Lymphovascular invasion and progesterone receptor status were found to be independent prognostic factors for mortality.

Conclusion: A lot of studies have been conducted, and criteria have been determined for breast cancer prognosis and survival. In our results, lymphovascular invasion and progesterone receptor status were found to be independent prognostic markers for both recurrence and mortality. More reliable results can be obtained with prospective study analyses.

Keywords: Prognostic factor, survival, breast cancer

INTRODUCTION

According to data from the World Health Organization, breast cancer is the most common cancer in women, both in the world and in Türkiye, and causes the highest mortality. This result was found to be the same for women over 40 years of age.[1] Therefore, prognostic factors and the survival of breast cancer gain importance.

Breast cancer treatment is constantly being renewed with current approaches. This situation varies according to the patient's age, comorbidities, immunohistochemical subtype of the tumor, receptor status, and stage of the cancer.[2]

Many studies have been conducted to determine the factors affecting the prognosis and survival of breast cancer. It is also known that prognosis differs in young and elderly patients.[3] Young age is considered to be younger than 40 years, and it has been demonstrated that tumor biology and outcomes differ.[4]

Many factors have been found to affect breast cancer prognosis and survival. These factors include age, hormone receptors, histological subtype, molecular subgroup, grade, perineural invasion (PNI) status, lymphovascular invasion (LVI) status, Ki-67 percentage, lymph node metastasis, distant metastasis, tumor size, stage, and treatments applied to the patient.[5-7]

We know that prognostic factors and gene assay are effect the treathment of the breast cancer. In addition, studies on gene assay have shown that in older and younger patients

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different genes have prognostic effectiveness.[8] In another study, it was determined that the survival results after recurrence of patients with close follow-up and the control group were different, and that close follow-up had an effect on survival.[9]

In this study, we aimed to analyze the prognostic factors and survival outcomes of breast cancer patients aged 40 years and older. We believe that these prognostic factors will be effective in the treatment and follow-up of the patient.

METHODS

The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 31.12.2020, Decision No: 2020/717). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 1187 patients aged 40 years and older who were operated on at Ondokuz Mayıs University Department of General Surgery, between August 2005 and April 2019 and whose data were accessed were included. Patient information was obtained from the automation system, the online database of the Ministry of Health, the hospital archive, and patients and/or their relatives. Patients whose data could not be accessed were not included in the study.

Patients were classified separately according to the type of surgery performed, axillary metastasis status (according to radiological status if axilla surgery was not performed) (positive or negative), axilla surgery performed (sentinel lymph node biopsy or axillary lymph node dissection), pathological tumor size (pT0, pT1, pT2, pT3, pT4), pathological lymph node number (pN0, pN1, pN2, pN3), pathological stage (stage 0, stage 1, stage 2, stage 3, stage 4), pathological grade (grade1, grade 2, grade 3), lymphovascular and perineural invasion status (positive or negative), hormone receptor status (positive or negative), C-erb B2 status (positive or negative), Ki-67 percentage, histopathological types (ductal carcinoma in situ, invasive ductal carcinoma, invasive lobular carcinoma and others), and molecular subgroup (luminal A, luminal B, Her-2 positive, triple negative). Prognostic factors were analyzed both in terms of recurrence and mortality as well as survival analysis as univariate and multivariate analysis.

We used TNM staging. For hormone receptor status, even 1% positivity was accepted positive group. In immunohistochemical tests, C-erb b2 status was accepted negative if it is 0 or 1+ and positive if 3+. We used FISH results if it is 2+. In distinguishing molecular subgroups, we paid attention to C-erb B2 status and Ki-67 percentage to differentiate luminal A and luminal B. We accepted the Ki-67 cut-off value as 14% in our study.

Statistical Analysis

Statistical analyses were performed with IBM SPSS V22 (Chicago, USA). Categorical variables were compared with the chi-square test. Normality analysis of quantitative data was performed with the Kolmogorov-Smirnov test. The Ki-67 percentage did not follow a normal distribution and it was compared with the Mann-Whitney U test. It was accepted as the starting surgery date for the follow-up period. The first detected locoregional recurrence or distant metastasis was accepted the endpoint event for disease free survival (DFS). A new cancer in the contralateral breast after 5 years from first diagnosis is considered a different cancer. The death of the patient was accepted the endpoint event for survival. Survival analysis was performed with the Kaplan-Meier test. Variables with a significant effect on OS or DFS were identified in univariate analysis. Then, these variables were subjected to multivariate analysis using the cox regression test. Results were reported as independent prognostic factors. Data were presented as mean±standard deviation, n (%), and 95% confidence interval. Statistical significance was accepted as $p<0.05$.

RESULTS

Of the 1187 patients included in the study, 4 were male and 1183 were female. Histopathologic type, presence or absence of pathologic involvement of axillary lymph nodes, estrogen receptor (ER) positivity, progesterone receptor (PR) positivity, Her-2/neu status, PNI, LVI status, and Ki-67 percentage were statistically significant in terms of both recurrence and mortality (**Figure 1**, **Table 1**).

Patients were divided into three age groups: 40-69, 70-79, and 80 and above. There was no statistical difference between age groups in terms of recurrence, but a significant difference was observed in terms of mortality.

In the analysis in terms of molecular subgroup, there was no statistical difference between luminal A and luminal B in terms of recurrence and between the Her-2 positive group and triple negative group in terms of mortality, but a significant difference was observed between the other groups. The luminal A group had the lowest recurrence rate, and the luminal B group had the lowest mortality rate.

There was a statistically significant difference between the type of surgery, surgical intervention in the axilla, recurrence, and mortality. However, considering that the type of surgery was chosen according to the patient's stage, tumor size, whether the patient received neoadjuvant chemotherapy (NAC) or not, and patient preference, it was thought that it would be more appropriate to be determined by randomized controlled studies.

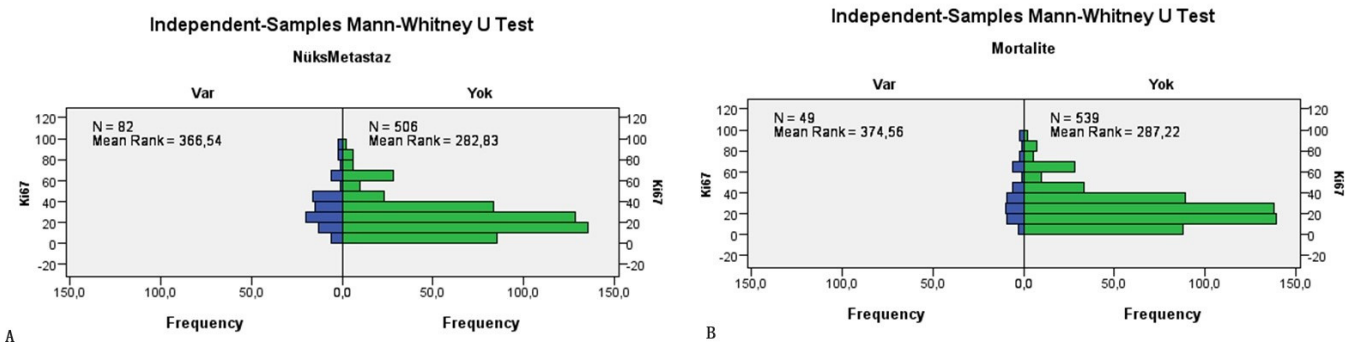

Figure 1. A-Comparison of Ki-67 and recurrence; B-Comparison of Ki-67 and mortality

Table 1. Comparison of individual variables in terms of recurrence and mortality

			Recurrence			Mortality		
			No	Yes	p	No	Yes	p
Histopathologic Type								
DCIS			58 (%96.7)	2 (%3.3)	<0.001	59 (98.3%)	1 (1.7%)	0.004
Invasive Ductal			759 (%79.3)	198 (%20.7)		780 (81.5%9)	177 (18.5%)	
Invasive Lobular			52 (%74.3%)	18 (%25.7)		58 (82.9%)	12 (17.1%)	
Others			90 (%90.0)	10 (%10.0)		88 (88.0%)	12 (12.0%)	
Pathologic axillary involvement								
Negative			547 (%88.8)	69 (%11.2)	<0.001	553 (%89.8)	63 (%10.2)	<0.001
Positive			362 (%71.3)	146 (%28.7)		384 (%75.6)	124 (%24.4)	
ER								
Negative			159 (%71.0)	65 (%29.0)	<0.001	162 (%72.3)	62 (%27.7)	<0.001
Positive			793 (%82.9)	164 (%17.1)		819 (%85.6)	138 (%14.4)	
PR								
Negative			258 (%72.5)	98 (%27.5)	<0.001	262 (%73.6)	94 (%26.4)	<0.001
Positive			692 (%84.1)	131 (%15.9)		717 (%87.1)	106 (%12.9)	
Her-2/neu								
Negative			637 (%82.4)	136 (%17.6)	0.005	654 (%84.6)	119 (%15.4)	0.015
Positive			258 (%75.4)	93 (%24.6)		298 (%78.8)	80 (%21.2)	
PNI								
Negative			624 (%84.0)	119 (%16.0)	<0.001	637 (%85.7)	106 (%14.3)	0.012
Positive			135 (%71.4)	54 (%28.6)		148 (%78.3)	41 (%21.7)	
LVI								
Negative			541 (%87.4)	78 (%12.6)	<0.001	552 (%89.2)	67 (%10.8)	<0.001
Positive			266 (%69.5)	117 (%30.5)		281 (%73.4)	102 (%26.6)	
Age group								
40-69			852 (%80.1)	212 (%19.9)	0.259	900 (%84.6)	164 (%15.4)	<0.001
70-79			84 (%85.7)	14 (%14.3)		70 (%71.4)	28 (%28.6)	
80+			22 (%88)	3 (%12)		15 (%60)	10 (%40)	
Molecular Subgroup								
Luminal A			400 (84.0%)	76 (16.0%)	<0.001	401 (84.2%)	75 (15.8%)	<0.001
Luminal B			386 (80.4%)	94 (19.6%)		410 (85.4%)	70 (14.6%)	
Her-2 +			77 (70.6%)	32 (29.4%)		81 (84.3%)	28 (25.7%)	
Triple neg.			61 (70.1%)	26 (29.9%)		61 (70.1%)	26 (29.9%)	
Types of axilla operation								
SLNB			639 (88%)	87 (12%)	<0.001	656 (90.4%)	70 (9.6%)	<0.001
ALND			269 (68.3%)	125 (31.7%)		278 (70.6%)	116 (29.4%)	
SLNB		Pat. LAP			0.009			
		Negative	506 (%89.7)	58 (%10.3)		517 (%91.7)	47 (%8.3)	
		Pat. LAP						0.026
		Positive	133 (%82.1)	29 (%17.9)		139 (%85.8)	23 (%14.2)	
ALND		Pat. LAP			0.063			
		Negative	39 (%79.6)	10 (%20.4)		33 (%67.3)	16 (%32.7)	
		Pat. LAP						0.598
		Positive	229 (%66.4)	116 (%33.6)		245 (%71)	100 (%29)	
SLNB		NAC			<0.001			
		Negative	561 (%91.5)	52 (%8.5)		558 (%91)	55 (%9)	
		NAC						0.155
		Positive	78 (%69)	35 (%31)		98 (%86.7)	15 (%13.3)	
ALND		NAC			<0.001			
		Negative	229 (%72.5)	87 (%27.5)		233 (%73.7)	83 (%26.3)	
		NAC						0.005
		Positive	39 (%50)	39 (%50)		45 (%57.7)	33 (%42.3)	
Grade								
	Grade1		93 (%94.9)	5 (%5.1)		88 (%89.8)	10 (%10.2)	
	Grade2		502 (%81.4)	115 (%18.6)	<0.001	513 (%83.1)	104 (%16.9)	0.148
	Grade3		346 (%76.5)	106 (%23.5)		369 (%81.6)	83 (%18.4)	
Pathological tumor size								
T0			88 (%87.1)	13 (%12.9)		94 (93.1%)	7 (6.9%)	
T1			390 (%86.3)	62 (%13.7)		401 (88.7%)	51 (11.3%)	
T2			415 (%81.1)	97 (%18.9)	<0.001	418 (81.6%)	94 (18.4%)	<0.001
T3			48 (%57.1)	36 (%42.9)		51 (60.7%)	33 (39.3%)	
T4			16 (%43.2)	21 (%56.8)		20 (54.1%)	17 (45.9%)	
T0		Pat. LAP						
		Negative	59 (%88.1)	8 (%11.9)		62 (%92.5)	5 (%7.5)	
T1		Pat. LAP						
		Negative	265 (%89.8)	30 (%10.2)		270 (%91.5)	25 (%8.5)	
T2		Pat. LAP			0.494			0.006
		Negative	202 (%88.2)	27 (%11.8)		203 (%88.6)	26 (%11.4)	
T3		Pat. LAP						
		Negative	202 (%88.2)	27 (%11.8)		203 (%88.6)	26 (%11.4)	
T4		Pat. LAP						
		Negative	17 (%89.5)	2 (%10.5)		15 (%78.9)	4 (%21.1)	
Number of removed lymph nodes								
SLNB			637 (%88.1)	86 (%11.9)	<0.001	653 (%90.3)	70 (%9.7)	
ALND<10			133 (%72.7)	50 (%27.3)		141 (%77)	42 (%23)	<0.001
ALND>10			139 (%63.8)	79 (%36.2)		143 (%65.6)	75 (%34.4)	
pN								
N0			553 (%88.8)	70 (%11.2)		559 (%89.7)	64 (%10.3)	<0.001
N1			268 (%80)	67 (%20)		273 (%81.5)	62 (%18.5)	
N2			71 (%61.7)	44 (%38.3)	<0.001	82 (%71.3)	33 (%28.7)	
N3			23 (%40.4)	34 (%59.6)		29 (%50.9)	28 (%49.1)	
Stage								
Stage 0			81 (%95.3)	4 (%4.7)		83 (%97.6)	2 (%2.4)	
Stage 1			279 (%91.2)	27 (%8.8)		284 (%92.8)	22 (%7.2)	
Stage 2			482 (%87.5)	69 (%12.5)	<0.001	472 (%85.7)	79 (%14.3)	<0.001
Stage 3			116 (%60.7)	75 (%39.3)		131 (%68.6)	60 (%31.4)	
Stage 4			0 (%0)	54 (%100)		15 (%27.8)	39 (%72.2)	

Patients who underwent sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) were analyzed separately according to the presence or absence of pathologic involvement. While there was a statistical difference in both recurrence and mortality in patients who underwent SLNB, no significant difference was observed in patients who underwent ALND. Again, patients who underwent SLNB and ALND were analyzed according to whether they received NAC or not. In both groups, a statistical difference was observed in terms of recurrence after receiving NAC, while a significant difference was observed in terms of mortality only in patients who underwent ALND.

There was a significant difference between grade and recurrence, but no significant difference between grade and mortality.

In the comparison between pathological tumor size and recurrence, pT0, pT1, and pT2 were similar among themselves; pT3, and pT4 were similar among themselves; in terms of mortality, pT0, pT1, pT3, and pT4 were similar among themselves, while there was a statistical difference between the other groups. When patients without axillary metastasis were re-examined in terms of pathological tumor size, a statistical difference was observed between pT4 and the others only in terms of mortality.

In the analysis, according to the number of lymph nodes dissected from the axilla, the groups with less than 10 lymph nodes and more than 10 lymph nodes were similar in terms of recurrence, while a significant difference was observed between these groups with SLNB. In terms of mortality, there was a difference between all groups. According to the number of lymph nodes with pathologic involvement, there was a significant difference between all groups in terms of recurrence. In terms of mortality, pN1 and pN2, pN2 and pN3, were similar, while a significant difference was observed between the other groups.

Table 1. Comparison of variables in terms of 5-year survival and disease-free survival

	5-year survival			5-year disease-free survival		
	Rate	Average duration (month)	p	Rate	Average duration (month)	p
Total patients	%88.8	55.9		%83.4	52.6	
Histopathologic type						
DCIS	%100		p=0.011	%96.7	59.7	
Invasive Ductal	%87.9	55.6		%81.6	51.7	
Invasive Lobular	%85.7	54.3		%84.3	53.0	p=0.002
Others	%93	57.9		%92	56.6	
Pathologic axillary involvement						
Negative	%94.6	58.1	p<0.001	%90.3	56.1	p<0.001
Positive	%82.7	54.0		%75.8	49.1	
ER						
Negative	%78.6	51.7	p<0.001	%72.3	47.6	p<0.001
Positive	%91.1	56.9		%85.9	53.8	
PR						
Negative	%80.9	53.0	p<0.001	%74.2	48.8	p<0.001
Positive	%92.1	57.2		%87.2	54.2	
Her-2/neu						
Negative	%89.7	56.1	p=0.138	%85.1	53.1	p=0.007
Positive	%86.2	55.3		%78.3	50.9	
PNI						
Negative	%89.8	56.0	p=0.238	%85.7	53.7	p=0.003
Positive	%85.7	56.0		%76.7	49.0	
LVI						
Negative	%92.6	57.2	p<0.001	%89	55.0	p<0.001
Positive	%82.5	54.0		%74.4	48.7	
Molecular Subgroup						
Luminal A	%91.2	56.9	p<0.001	%88.2	54.6	p<0.001
Luminal B	%89.6	56.2		%82.1	52.1	
Her-2 +	%82.6	53.7		%72.5	48.3	
Triple negative	%75.9	50.2		%71.3	46.5	
Grade						
Grade1	%94.9	59.0	p=0.009	%95.9	57.9	
Grade2	%89.6	56.3		%84.9	53.5	p<0.001
Grade3	%86.3	54.7		%78.1	49.9	
Pathological tumor size						
T0	%95	57.7	p<0.001	%87.1	54.6	
T1	%92.5	57.4		%88.1	54.7	
T2	%89.8	56.5		%84.2	53.2	p<0.001
T3	%67.9	47.9		%61.9	42.2	
T4	%59.5	45.5		%54.1	36.0	
pN						
N0	%94.5	58.0	p<0.001	%90.2	56.1	p<0.001
N1	%87.5	55.1		%82.4	51.5	
N2	%77.4	53.4		%67.8	45.7	
N3	%66.7	50.0		%54.4	42.8	
Stage						
Stage 0	%98.8	59.5	p<0.001	%95.3	58.6	
Stage 1	%95.8	58.6		%92.8	57.2	
Stage 2	%92.6	57.3		%89.7	56.0	p<0.001
Stage 3	%77	52.9		%68.1	47.7	
Stage 4	%37	33.9		%1.9	0.0	

In terms of stage, stages 0, 1, and 2 were similar in terms of recurrence, and stages 1 and 2 were similar in terms of mortality, while a significant difference was observed between the other groups.

The 5-year disease-free survival rate was 88.8% and the mean survival time was 55.9 months, while the 5-year disease-free survival rate was 83.4% and the mean disease-free survival time was 52.6 months. In individual analyses, PNI and Her-2 neu status were statistically significant only in terms of disease-free survival, while LVI, ER, PR positivity, Ki-67 percentage, grade, tumor diameter, lymph node involvement and number of involved lymph nodes, stage, molecular subgroup, and histological type were statistically significant in terms of both survival and disease-free survival. In the multivariate analysis, excluding the type of surgery and NAC status, which disrupted the homogeneous distribution, PNI, LVI, grade, and PR positivity were found to be independent factors for recurrence, while LVI and PR positivity were found to be independent factors for mortality (**Table 2**).

DISCUSSION

Since breast cancer is the most common cancer in women, it has been of great importance, and much research has been done on it in the world and in Turkey. In history, it started with catastrophic surgeries such as radical mastectomy, and with the discovery and development of treatments such as chemotherapy, radiotherapy, and hormone therapy, more moderate surgeries were performed. Today, oncoplastic surgery and protocols with very good aesthetic results are applied to appropriate patients.

It has been and continues to be investigated which treatment will be more beneficial for patients, the expected recurrence and mortality rates in the future, and which treatments can minimize them. In this respect, prognostic factors gain importance. In addition, some of the prognostic factors are also important in terms of directing the treatment choices of patients.[10,11]

Many models have been established for prognostic factors determining mortality and recurrence.[12,13] Phung et al.[13] conducted a study examining these models and found that the most commonly used predictors in these models were tumor size, nodal involvement, age, grade, and ER status. In our study, these factors were found to be statistically significant, and grade was found to be an independent factor in terms of recurrence.

In the Makower et al.[14] study, factors associated with poor survival were found to be LVI, axillary involvement, tumor size, grade, and comorbid diseases, and LVI was found to be a prognostic marker in N0 patients. In a cohort study conducted in China, tumor size, grade, LVI, number of metastatic lymph nodes, and hormone receptor status were found to be associated with both survival and disease-free survival, whereas age, distant metastasis, and Ki-67 percentage were only associated with survival.[15] In other studies, LVI was found to be an independent prognostic factor for survival and disease-free survival in early breast cancer.[16-18] In our study, LVI was found to be an independent prognostic factor for both recurrence and mortality.

PR is an important receptor involved in both normal mammary gland development and breast carcinogenesis.[19] PR also plays an important role in determining the molecular subtype of breast cancer and in the effectiveness of hormonotherapy.[20] PR positivity has been reported to affect the response to hormone therapy and therefore has a prognostic effect.[21] A meta-analysis revealed that ER and PR loss were significantly associated with prognosis in terms of survival and survival after recurrence.[22]

Perineural invasion was found to be an independent prognostic factor in our study, as in the study by Hosoya et al.[23] In another study, multivariate analysis of prognostic factors revealed a significant association between PNI and locoregional recurrence.[24]

Study Limitations

Although the count of patients is high, the patient distribution is not homogeneous. Therefore, the possibility of prognostic factors being affected by each other increases. Although independent factors are identified by performing multivariate analyses, we think that analyzes on more homogeneously distributed patient groups or prospective studies will provide better information.

CONCLUSION

In this study, PNI, LVI, grade, and PR status were found to be independent prognostic factors for recurrence, while LVI and PR status were found to be independent prognostic factors for mortality. We think that regulating follow-up and treatment by taking these factors into consideration will improve survival and disease-free survival. In addition, it will allow us to make predictions in terms of close follow-up of patients, thus indirectly affecting survival.

Acknowledgements

I would like to thank Prof. Dr. Necati Özen, Prof. Dr. Bekir Kuru, and all my professors for their support during the production of this study, and Assoc. Prof. Dr. Ramazan Topçu for his support during the writing phase.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 31.12.2020, Decision No: 2020/717).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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